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CURRENT STATUS IN MANAGEMENT OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) IN REPUBLIC OF MACEDONIA

СЕГАШНА СОСТОЈБА ВО ТРЕТМАНОТ НА БОЛНИТЕ СО ХРОНИЧНА ЛИМФАТИЧНА ЛЕУКЕМИЈА (ХЛЛ) ВО РЕПУБЛИКА МАКЕДОНИЈА

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Abstract

Chronic lymphocytic leukemia (CLL) is the most commonly diagnosed type of leukemia in Western Europe and North America, and represents about 30% of all leukemias in adults. CLL is a disease of elderly, who often have multiple comorbidities. These factors affect further treatment decisions, despite the great progress in the therapy of CLL in the last two decades.
The aim of this study was to evaluate the current status in the management of patients with CLL in the Republic of Macedonia and to compare it with CLL patients in other western countries.
We analyzed 102 patients with CLL referred to our Institution for control and/or treatment in the period from January 2015 to October 2015. Median age of our group of patients at the time of diagnosis was 62.7 years with almost 40% of patients older than 64 years. Male to female ratio was 1.3:1 and 54% of patients were diagnosed in stage "0" according to Rai staging system. Watch and wait was the most common treatment approach (58.8%) at the time of diagnosis, but at the moment of analysis only 33% of patients were still without treatment. The most common treatment in this group of CLL patients was FCR protocol with 39.5% of patients treated with an average of 5 cycles of this immunochemotherapeutic regimen. The average time of progression free survival (PFS) in all treated patients was 32.8 months with range between 2-72 months.
In summary, clinical characteristics of CLL patient in our clinical settings and the most common therapeutic approach at our Institution do not differ significantly from the characteristics of the average CLL patient in other studies.

Key words: chronic lymphocytic leukemia, treatment, FCR

Апстракт

Хроничната лимфатична леукемија (ХЛЛ) е најчест тип на леукемија во Западна Европа и Северна Америка и претставува 30% од леукемиите кај возрасните. ХЛЛ е болест на повозрасната популација, која често има мултипни коморбидитети. Овој фактор во голема мера влијае на терапискиот избор и покрај големиот напредок во третманот на ова заболување во последните две децении.
Цел на овој труд е евалуација на сегашната состојба во третманот на пациентите со ХЛЛ во Република Македонија и споредба со третманот на ова заболување во другите западни земји.
Анализиравме 102 пациенти со ХЛЛ кои се јавиле за контрола и/или терапија, на нашата Клиника во период од јануари 2015 до октомври 2015 година. Медиана на возраста во нашата група на болни во моментот на поставување на дијагнозата беше 62,7 години и речиси 40% од пациентите беа постари од 64 години. Сообносот мажи спрема жени беше 1,3:1 и речиси 54% од болните беа дијагностицирани во "О" стадиум според Rai стејџинг системот. Опсервацијата на болните беше најчестиот тип на тераписки пристап (58.8%) во моментот на поставување на дијагнозата, додека во моментот на анализа на пациентите од ова група само 33% беа сè уште без третман. Најчест тип на третман во нашата испитувана група беше FCR протоколот и 39,9% од болните беа третирани со просечно 5 циклуса на овој имунохемотераписки протокол. Просечно траење на периодот без прогресија на болест кај лекуваните пациенти изнесуваше 32,8 месеци (2-72 месеци).
Клиничките карактеристики и терапискиот пристап на најголем број пациенти со ХЛЛ во нашата институција не се разликуваат сигнификантно во споредба со карактеристиките и третманот на болните со ХЛЛ во другите студии.

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Клучни зборови: хронична лимфатична леукемија, третман, FCR.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in Western Europe and North America, with an incidence of 4.1/100,000 inhabitants [1-3]. CLL affects mainly older and male patients; the median age at diagnosis is 67-72 years [3] and almost 70% of patients are older than 65 years. Because the incidence rises with age, it is projected that the CLL prevalence will increase in the forthcoming years due to the constant aging of the population [1,2].

The diagnosis of CLL is established when the blood count shows a lymphocytosis with >5.000/μl clonal B-lymphocytes, a peripheral blood smear with small, morphologically mature lymphocytes with immunophenotype characterized by the coexpression of CD5 and B-cell surface antigens CD19, CD20, CD 23 and clonal expression of either kappa or lambda immunoglobulin light chains [4]. These clonal mature B cells can accumulate in the peripheral blood and bone marrow, as well as the lymph nodes, liver and spleen. Nowadays, mandatory diagnostic tests for CLL are complete blood count with peripheral blood smear and immunophenotyping of the lymphocytes with flow cytometry. Diagnostic tests like bone marrow biopsy, lymph node biopsy and cytogenetic evaluation are not necessary for diagnosis, but are recommended to differentiate autoimmune cytopenia from cytopenia resulting from bone marrow infiltration, in case of Richter transformation or to define some genetic risk factors.

The clinical course of CLL is very heterogeneous. Some patients do not need treatment for many years, while others have rapidly progressive disease requiring immediate treatment. The clinical staging system by Binet [5] and Rai [6] were introduced decades ago and are still widely used as simple and inexpensive tools to distinguish which patients should be treated or managed with a watch and wait approach (Table 1). Both staging systems require clinical examination of the lymph node, spleen, liver enlargement and blood count. Treatment should be initiated in patients with advanced CLL (Binet stage C or Rai stages III/IV), which are defined by a thrombocytopenia and/or anemia, related to bone marrow infiltration. Treatment is also indicated in case of constitutional symptoms, such as weight loss, night sweats, fever, rapid lymphocyte doubling time and/or symptomatic enlargement of lymph nodes or spleen [4].

Table 1. Staging systems in CLL

BINET Stage	**Features**
A	<3 Lymphoid areas*
B	>3 Lymphoid areas
C	Hemoglobin <100 g/L or platelet count <100x10^9 /L
RAI Stage	
0	Lymphocytosis only
I	Lymphadenopathy
II	Hepatomegaly or splenomegaly with lymphocytosis
III	Anemia (Hemoglobin <110 g/L)
IV	Platelet count <100x10^9 /L

*The five lymphoid areas comprise: uni or bilateral cervical, axillary and inguinal lymphoid, hepatomegaly and splenomegaly

Both staging systems lack the accuracy to predict CLL outcome on an individual basis. Therefore, many molecular and biological factors were proposed for predictiton of disease progression and survival [7] and continuous attempts are made to define the most relevant prognostic factors [8]. These factors include the mutational status of immunoglobulin heavy chain [9], the expression of ZAP-70 protein in CLL cells [10], the expression of CD 38 antigen [11], but the most important practical significance have the cytogenetic abnormallities, especially 17p deletions and TP53 gene mutations [12,13]. The presence of a deletion of the short arm of the chromosome 17p or TP53 mutations are associated with a poor prognosis and resistance to most chemotherapeutic agents. Treatment decisions in CLL patients depend not only on these prognostic factors, but even more on the patient's physical fitness, comorbidities and concomitant medical treatment. According to these patient's characteristics, we can divide CLL patients in three groups "go go"; "slow go" and "no go". The first group consists of physically fit patients without or with mild comorbidities and they should be treated with the standard treatment that includes FCR protocol. The second group "slow go" includes patients with relevant comorbidities that impact the life expectancy and should be treated with reduced-intensity protocols. The third group are "no go" patients with markedly reduced life expectancy due to multiple and severe comorbidites, who should be treated with the best supportive treatment.

The standard first-line treatment for younger or older but fit CLL patients (the so-called "go go") nowadays is immunochemotherapy with purine analogues (fludarabine or cladribine), cyclophosphamide and anti-CD20 monoclonal antibodies-rituximab (FCR regimen). It is recommended to give 6 cycles of FCR, as it increases the probability of eradication of minimal residual disease (MDR) and improves the progression-free survival (PFS) and overall survival (OS) [13-15].

Treatment of patients with relevant comorbidities (the so-called "slow go") includes therapy with chlorambucil or bendamustine and anti-CD20 monoclonal antibodies-rituximab [16]. The combination of chlorambucil or bendamustine and ofatumumab or obinutuzumab, another anti-CD20 monoclonal antibodies which might have a higher complement-dependent cytotoxicity (CDC) than rituximab, offers safe and effective treatment of this

group of patients [17,18]. Treatment of refractory and relapsed fit patients nowadays includes novel agents like ibrutinib (Bruton's tyrosine kinase-BTK inhibitor) and idelalisib (phasphatidylinositol-3-kinase inhibitor) or allogeneic stem cell transplantation for young patients refractory to first-line therapy [19-21].
The aim of this study was to evaluate the current status in the management of patients with CLL in the Republic of Macedonia and to compare it with CLL patients in other western countries.

Materials and methods

We analyzed 102 patients with CLL referred to our Institution for control and/or treatment in the period from January 2015 to October 2015. All patients were diagnosed at the University Clinic for Hematology in Skopje, R. Macedonia in the period between 1997-2015 with standard diagnostic procedures according to the recommendation of IWCLL (International Workshop on Chronic Lymphocytic Leukemia) [4].
Data collected from medical records were: age at diagnosis, gender, clinical stage by Rai, symptoms, type of treatment, period without progression of disease with or without treatment. The data were analyzed using standard statistical tests in Microsoft Office Excel 2003 and SSPP 7.

Results

Median age of our group of patients at the time of diagnosis was 62.7 years with 39/102 (38%) patients older than 64 years. Age distribution of patients with CLL at the time of diagnosis is presented in Figure 1. Only 3 patients were younger than 45 years, 15 patients were between 45-54 years old, 45 patients were between 55-64 years old, 29 patients were between 65-74 years old and 10 patients were older than 75 years. Average life expectancies in the Republic of Macedonia are 76 years; 73 for men and 78 years for women. Median age of patients with CLL in our group was 62.7 years at the time of diagnosis. Male to female ratio in our group of patients was 1.3:1 and 58/102 (56.9%) patients were male. Distribution of the patients according to Rai staging system is presented in Figure 2 and 55/102 (54%) patients were in the early stage of disease (Rai grade "O"), 21 patients were in grade "1", 5 patients were grade "2", 16 patients grade "3" and 5 patients grade "4" (Figure 2). In our group of patients 81% had at least one comorbidity and the most common were cardiovascular diseases.

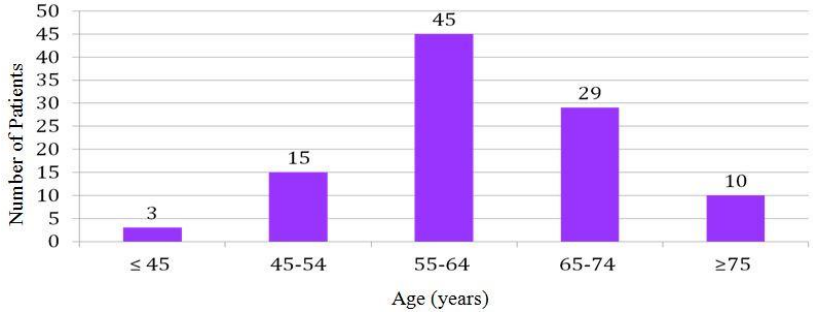

Fig. 1. Age distribution of CLL patients at the time of diagnosis

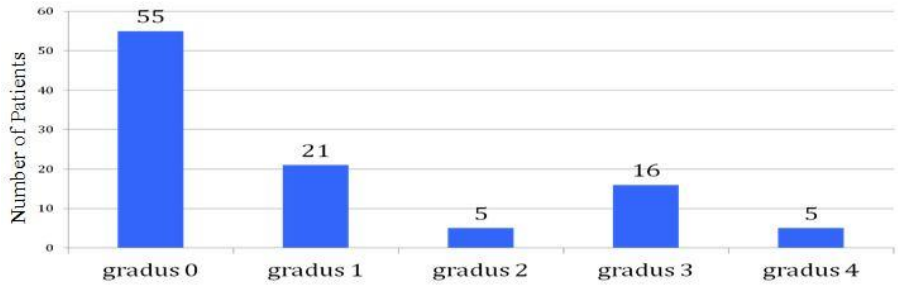

Fig. 2. Distribution of CLL patients according to Rai staging system at the time of diagnosis

Watch and wait was the most common treatment approach at the time of diagnosis with 58.8% of patients (59/102) who did not require therapy at the time of diagnosis. At the moment of analysis only 33% of patients were still without treatment. Average time of observation without treatment in our group of patients was 3.6 years, with range between 0-18 years. Overall time from diagnosis was 7.3 years, with range between 0-18 years.

The most common treatment modality in our group of CLL patients was FCR protocol with 39.5% of patients treated with average of 5 cycles of this immunochemotherapeutic regimen. The second most common treatment option was monotherapy with chloramubucil and the third was R-CVP immunochemotherapeutic regimen (Figure 3). Average time of progression free survival (PFS) in all treated patients was 32.8 months with

range between 2-72 months. Average time of PFS in patients treated with FCR was 35.1 months (range: 12-72+ months), compared to 18.6 months (range: 2-30) in patients treated with R-CVP protocol (Table 2). These results confirmed the superiority of FCR as a therapeutic regimen versus R-CVP.

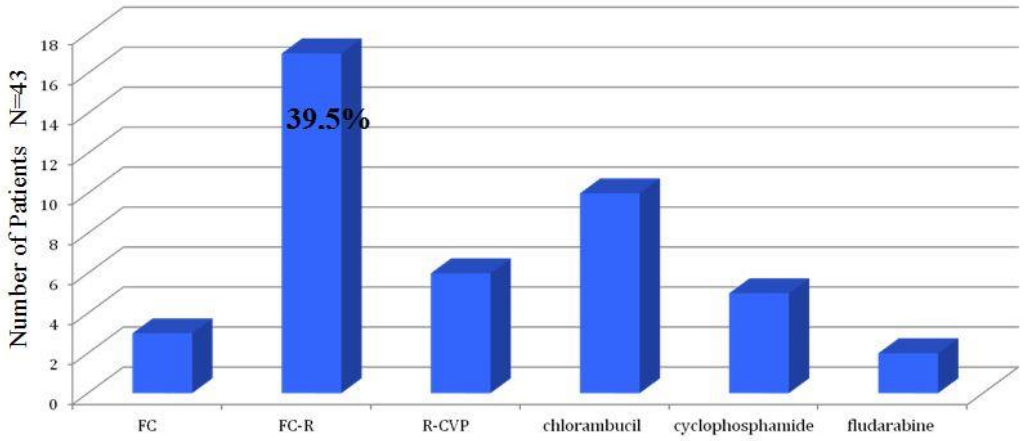

Fig. 3. Distribution of CLL patients according to treatment options
FC = fludarabine+cyclophosphamide, FCR = fludarabine+cyclophosphamide+rituximab, R-CVP = rituximab+cyclophosphamide+vincristine+prednisolone

Table 2. Progression free survival in different treatments in CLL patients

Treatment	No patients	Mean Age	Mean No of cycles	PFS months	Range months
FCR	17(39.5%)	62.4	4.3	35.1	12-72+
R-CVP	6(14%)	65.6	6.1	18.6	2-30

Discussion

Population studies show that the median age at diagnosis of CLL patients is 71 years in USA and 70 years in Europe, while in clinics the median age at diagnosis is much younger (64 years at the Mayo Clinic; 58 years at MD Anderson Cancer Center) [22,23]. In our study, the median age at diagnosis of the referred patients was also younger (62.7 years) than the reported one. The median age of CLL clinic patients is relatively close to the population median age, but there are still a substantial number of elderly patients in the nonreferred group. This suggests that younger patients are more often being referred to the clinic for therapy, while elderly patients may not be referred as they are considered not fit enough for treatment.

Distribution of the patients according to Rai staging system in our study was similar to that reported in the literature [4-6], as well as the sex distribution [3]. Male sex is prevailing in CLL patients and early stages of disease are more common at the time of diagnosis. Comorbidities are very common in CLL patients due to the advanced age of these patients. A typical CLL patient is older than 65 years; she/he has three different comorbidities (most commonly cardiovascular disease, arthritis and psychiatric disease) and 44% of patients older than 65 years have some degree of renal insufficiency [24]. In our group of patients 81% had at least one comorbidity and the most common were cardiovascular diseases.

Observation was most common treatment approach at the time of diagnosis with 58.8% of patients not requiring therapy in the beginning, but later during the course of disease only 33% of patients were still without treatment. The average time of observation without treatment was 3.6 years, with range 0-18 years. Similar to other studies, the most common treatment was FCR protocol, with almost 40% of patients treated with this immunochemotherapeutic regimen. The average time of PFS in patients treated with FCR was 35.1 months (range: 12-72+ months). Almost 60% of patients requiring treatment in our study were treated with less aggressive therapeutic regimens due to the advanced age and/or comorbidities.

In summary, in this study we presented the most common clinical characteristics of an CLL patient in our clinical settings and the most common therapeutic approach at our Institution that do not differ signifycantly from the characteristics of CLL patient in other studies.

Conflict of interest statement. None declared.

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